Genetics

Peter J. Russell

Library of Congress Cataloging-in-Publication Data

Russell, Peter J.
Genetics.

Bibliography: p.
Includes index.
1. Genetics. I. Title.
QH430.R87 1989 575.1 88–26440
ISBN 0–673–39843–9

2 3 4 5 6 7 8 9 10—VHJ—95 94 93 92 91 90

Printed in the United States of America

Design and illustration development: J/B Woolsey Associates, Bala Cynwyd PA
Designer: Wladislawa Finne
Illustrators: Bette Woolsey, John D. Woolsey, Patrick Lane

Credits and Acknowledgments appear on page 893.

Cover illustration: This computer-generated graphic was created by Arthur J. Olson of the Research Institute of Scripps Clinic, La Jolla, California, using a Convex C1 minisupercomputer and a Silicon Graphics 4D Graphics Display, and the molecular surface rendering software MCS developed by Michael L. Connolly. Copyright © 1988.

Preface

Genetics has long been one of the key areas in biology, and in the twenty-five years since the first unravelings of the DNA mysteries, we have seen an unparalleled explosion of knowledge and understanding about genetics and its related disciplines. Not only is knowledge of genetics accumulating rapidly, but its many applications are affecting our daily lives and bringing benefit to humanity. In writing *Genetics*, my goal is to provide today's students with a necessary new synthesis of this vital field.

It is most gratifying when a project that has demanded a great deal of time and effort is successful. The first edition of *Genetics* has achieved such a positive response from its users that the publisher and I have invested our time and effort to improve that book so that we have a superior new edition. The second edition retains the overall approach, logical progression of ideas, organization, and pedagogical features (such as "Analytical Approaches for Solving Genetics Problems," "Keynotes") that made the first edition readily accessible to students. It retains too a format that allows you to use the chapters out of sequence to accommodate your own teaching strategies. Some significant changes, however, appear in this second edition:

1. All the molecular aspects of genetics are updated, so that the book continues to reflect our current understanding of genes at the molecular level.
2. Molecular approaches applied to the traditional, classical areas of genetics (such as diagnosis of human disease) have been developed in more detail.
3. Because recombinant DNA technology has revolutionized many areas of biology, a chapter is added, concentrating on recombinant DNA technology and the manipulation of DNA. This addition is significant in that it shows how, by manipulating DNA, many applications have become available for use in biological research, commercial ventures, and medical diagnoses. The first edition had some coverage of this topic, but I have expanded and updated it to reflect the most recent uses of this technology.

4. A new chapter on genetic recombination shows models for generating genetic change by crossover events.
5. The chapter on gene regulation in eukaryotes is significantly rewritten and expanded.
6. The chapters on genetics of populations and quantitative genetics are expanded and significantly strengthened by additional examples and by more comprehensive treatment of all topics.
7. The art program is completely revised. Many figures have been added, and all the original illustrations have been redrawn for greater clarity. The innovative new art program emphasizes key genetic processes, making genetics more accessible to students and pedagogically sound for instructors.
8. Many questions and problems are added to the chapters. All answers have been checked for accuracy by independent reviewers.
9. Many references have been added to the "Suggested Readings" that accompany each chapter.
10. Many of the first-edition "boxed" special topics have been integrated into the text so that these topics receive as much attention as all the other topics.

Organization and Coverage

The second edition's twenty-four chapters contrast to the first edition's eighteen. This change reflects added chapters as well as reorganized material. Dividing some of the chapters in two allows for greater clarity and depth of coverage.

The first seven chapters deal with transmission of the genetic material. In Chapter 1 we review the structure of viruses and of prokaryotic and eukaryotic cells, and asexual and sexual reproduction. Mitosis and meiosis are discussed in the context of both animal and plant life cycles. Chapter 2 is focused on the contributions Mendel made to our understanding of the principles of heredity, and Chapters 2 and 3 both present the basic principles of genetics in relation to Mendel's laws. Chapter 3 covers experimental evidence for the relationship between genes and chromosomes, methods of sex determination, and Mendelian genetics in human beings.

The exceptions to and extensions of Mendelian analysis (such as the existence of multiple alleles, lethal alleles, and modifications of dominance relationships) are described in Chapter 4. In Chapter 5, we describe how the order of and distance between the genes on eukaryotic chromosomes are determined in genetic experiments designed to quantify the crossovers that occur during meiosis. In the next two chapters, we consider advanced mapping analysis in eukaryotes, and genetic mapping in prokaryotes. (This material had been combined in one chapter in the first edition.) Chapter 6 is focused on tetrad analysis, primarily in fungal systems, on using mitotic analysis in mapping eukaryotic genes, and on procedures for mapping genes to human chromosomes by means of somatic cell hybrids. In Chapter 7, we discuss the ways of mapping genes in bacteriophages and in bacteria (transformation, conjugation, and transduction).

In Chapters 8 through 15, the "molecular core" of the book, we present the current state of knowledge on the molecular aspects of genetics. In Chapter 8, we cover the structure of DNA, and present the classical experiments revealing that DNA and RNA are genetic material, and the double helix model for the structure of DNA. In this edition, the details of DNA structure and the organization of DNA in chromosomes in prokaryotes are exposed in Chapter 9. We cover DNA replication in prokaryotes and eukaryotes in Chapter 10.

After thoroughly explaining the nature of the gene and its relationship to chromosome structure, we discuss the first step in the expression of a gene transcription. In this edition, we describe the general process of transcription in Chapter 11 and we present the currently understood details of the structure, transcription, and processing of messenger RNA, transfer RNA, and ribosomal RNA molecules for both prokaryotes and eukaryotes in Chapter 12. In Chapter 13, we describe the structure of proteins, the evidence for the nature of the genetic code, and a detailed expression of our current knowledge on translation in both prokaryotes and eukaryotes. In Chapter 14, we examine genetic fine structure and some aspects of gene function, such as genetic control of protein and enzyme structure and function, and involvement of particular sets of genes in directing and controlling biochemical pathways. In the new Chapter 15, on recombinant DNA technology, we discuss in detail the modern tools used in molecular genetics. Recombinant DNA technology for cloning and characterizing genes and manipulating DNA, are described followed by the commercial applications of recombinant DNA technology.

In the next four chapters, we describe the ways in which genetic material can change or be changed or both. The processes of gene mutation and the procedures which screen for potential mutagens and carcinogens (Ames test) and which select for particular classes of mutants from a heterogeneous population are discussed in Chapter 16. Chromosome aberrations—that is, changes in normal chromosome structure or chromosome number—are described in Chapter 17, and the structures and movement of transposable genetic elements in prokaryotes and eukaryotes are presented in Chapter 18. Models for generating genetic change by genetic recombination events are discussed in still another addition, Chapter 19.

The next two chapters are focused on regulation of gene expression in prokaryotes (Chapter 20) and eukaryotes (Chapter 21). In Chapter 20, we discuss the operon as a unit of gene regulation, the current molecular details in the regulation of gene expression in bacterial operons, and regulation of genes in bacteriophages. In Chapter 21, we explain how gene expression is regulated in eukaryotes by focusing on the molecular changes that accompany gene regulation, short-term gene regulation in lower and higher eukaryotes, gene regulation in development and differentiation, genetic defects in human development, and oncogenes and their relationship to cancer.

In Chapter 22, we address the organization and genetics of extranuclear genomes of mitochondria and chloroplasts. We cover the classical genetic experiments, which established that a gene is extranuclear. In this chapter we also discuss current molecular information about the organization of genes within the extranuclear genomes.

In Chapters 23 and 24, we describe quantitative genetics and the genetics of populations, respectively. In Chapter 23, we develop the concept that some heritable traits, the quantitative traits, show continuous variation over a range of phenotypes. In Chapter 23 we also discuss heritability: the relative extent to which a characteristic is determined by genes or by the environment. In Chapter 24, we present the basic principles in the genetics of populations and extend our treatment of the gene from the individual organism to a population of organisms.

Pedagogical Features

Because the study of genetics is so complex and difficult, I have incorporated a number of special pedagogical features to help students and enhance their understanding and appreciation of genetic principles:

1. Most chapters have a section on "Analytical Approaches for Solving Genetics Problems." The principles of genetics have always been best taught with a problem-solving approach. Often, however, beginning students do not acquire experience with the basic concepts that would enable them to methodically attack assigned problems. In the "Analytical Approaches" sections, typical genetic problems are "talked through" in step-by-step detail to help students understand how to tackle a genetics problem by applying fundamental principles.
2. More than 400 questions and problems in the problem sets closing each chapter give students further practice in solving genetics problems. For each chapter, the problems are chosen to represent a range of difficulty and topics. The answers to selected questions (indicated by *) are included at the back of the

book, and answers to all questions are available in a separate supplement.
3. Keynote summaries throughout each chapter emphasize important ideas and critical points.
4. Important terms and concepts are clearly defined where they are introduced in the text and are collected in a Glossary at the back of the book for easy reference.
5. Comprehensive and up-to-date bibliographies for each chapter are included at the back of the book.
6. Some chapters include boxes covering special topics related to chapter coverage. Some of these boxed topics are: *What Organisms Are Suitable for Use in Genetic Experiments* (Chapter 2); and *Equilibrium Density Gradient Centrifugation* (Chapter 10).

Acknowledgments

I would like to extend special thanks to Ben Pierce (Baylor University) for his creative rewritings of Chapter 23 and 24, "Quantitative Genetics" and "Genetics of Populations." He did an excellent job in expanding two very difficult topics, making a significant contribution to the overall quality of this book.

Also making an invaluable contribution to this text are John and Bette Woolsey of J/B Woolsey Associates, Inc., who developed and executed an art program that is innovative and exciting.

I want to again acknowledge my wife, Jenny, and my children, Steven and Kristie, for enduring the time I invested in this book. I am also grateful to my students of genetics here at Reed for their encouragement in this endeavor. I would also like to thank all the reviewers involved in this project, including: Fred W. Allendorf (University of Montana), Phillip T. Barnes (Connecticut College), John Belote (Syracuse University), Jean A. Bowles (Metropolitan State College), L. Herbert Bruneau (Oklahoma State University), Scott K. Davis (Texas A&M University), Max P. Dunford (New Mexico State University), Paul Goldstein (University of Texas, El Paso), J.L. Hamrick (University of Georgia), Duane L. Johnson (Colorado State University), Elliot Krause (Seton Hall University), Peter Kuempel (University of Colorado), E.N. Larter (University of Manatoba), Thomas J. Leonard (University of Wisconsin, Madison), Mark F. Sanders (University of California, Davis), Bruce A. Voyles (Grinnell College), William Wissinger, Ph.D. (St. Bonaventure University), Harry Wistrand (Agnes Scott College). For their time and effort in reviewing our new art program, I give special thanks to: Joseph O. Falkinham, III (Virginia Polytechnic Institute), Clint Magill (Texas A&M University), Jim Price (Texas A&M University) for their thorough examination of the material. I am grateful to the Literary Executor of the late Sir Ronald A. Fisher, F.R.S., to Dr. Frank Yates, F.R.S., and to Longman Group Ltd. London, for permission to reprint Table IV from their book *Statistical Table for Biological, Agricultural and Medical Research* (6th edition, 1974).

Finally, I thank everyone in Scott, Foresman/Little, Brown's College Division who contributed to this effort. They include Bonnie Roesch, Maxine Effenson, Jane Tufts, Janice Friedman, Cynthia Frank, Maryann Zoll, Julia Slater, and Jane Betz.

Contents

9 The Organization of DNA in Chromosomes 279

10 DNA Replication 315

11 Transcription 354

12 RNA Molecules and RNA Processing 371

13 The Genetic Code and the Translation of the Genetic Message 407

14
Genetic Fine Structure and Gene Function 436

15
Recombinant DNA Technology and the Manipulation of DNA 482

16
Gene Mutations 518

17
Chromosome Aberrations 550

22
Organization and Genetics of Extranuclear Genomes 699

23
Quantitative Genetics 734

24
Genetics of Populations 781

1

Viruses, Cells, and Cellular Reproduction

Genetics is the science of heredity and involves studying the structure, function, and transmission of genes (the units of heredity) from one generation to the next. The differences between organisms are the result of differences in the genes they carry, which have resulted from the evolutionary processes of mutation (a heritable change in the genetic material), recombination (exchange of genetic material between chromosomes), and selection (the favoring of particular combinations of genes in a given environment). In comparison with evolutionary time, very little time has been spent studying genetics. The principles of heredity were recognized by Gregor Mendel in the 1860s, the development of the subject began about 1900, and the key modern discoveries have been made in the past three or four decades.

The study of genetics has examined two aspects of the genetic material of living organisms: how physical traits are coded for and expressed in the organism, and how these traits are inherited (copied and passed on) from one generation to the next (Figure 1.1).

At present, we have a good understanding of the nature of genetic material, how it is replicated and passed on from generation to generation, how it is expressed in the cell, and how that expression is regulated. Clearly, gene activity is of central importance to cell growth and function and to the development and differentiation of organisms. In these respects the study of genetics interfaces directly with cellular biology, embryology, and developmental biology.

In the past decade genetics has received attention above and beyond its basic contributions to our understanding of life processes and of genetic diseases. This interest has come about from public attention given to the development and application of particular molecular techniques known collectively as *recombinant DNA technology*. Research in this area has led to the development of industries dealing in what is called *biotechnology*, or *genetic engineering*. While most of this research was undertaken to study fundamental genetic processes without regard to practical applications, there has been, and will continue to be, a lot of applied work

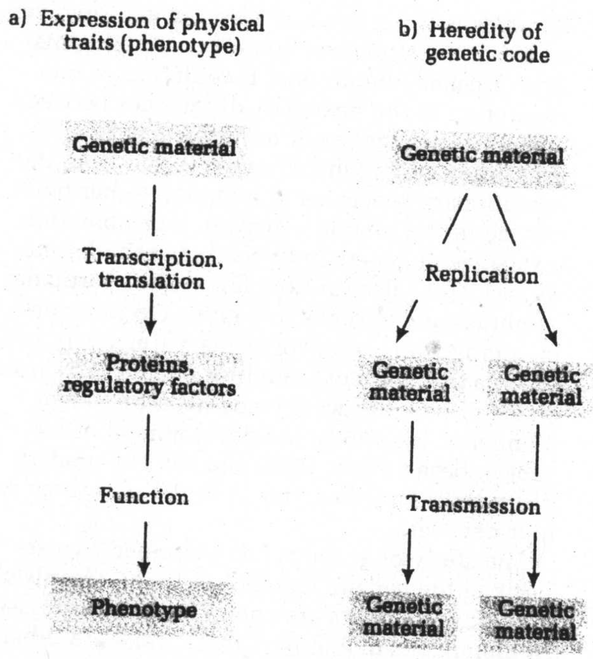

Figure 1.1 The two roles of genetic material: (a) coding for the physical traits (phenotype) of an organism through the processes of transcription, translation, and protein manufacture; (b) ensuring, through replication and division, that the organism's genetic code is accurately transmitted from one generation to the next.

done that is of direct benefit to humankind. In the area of plant breeding, genetic engineering is being applied to improve crop yields and to develop plants resistant to pests and plant diseases. In the area of animal breeding, genetic engineering is being employed in the beef, dairy cattle, and poultry industries to improve yields and to develop better strains. In medicine the potential is equally impressive. For example, recombinant DNA technology is proving very important in the production of antibiotics, hormones, and other medically important agents and in the diagnosis and treatment of certain human genetic diseases (such as Huntington's disease and Tay-Sachs disease). In short, the science of genetics is currently in a dramatic growth phase. By understanding the basic principles of genetics, as described in this text, you will have a greater capacity to understand, foster, and perhaps contribute to the new and exciting applications of this subject.

Viruses

A **virus** is a noncellular organism that can reproduce only within a host cell. It contains genetic material, either **DNA (deoxyribonucleic acid)** or **RNA (ribonucleic acid),** within a membrane or protein coat. Every type of cellular organism can be infected by viruses. Thus there are plant viruses, animal viruses, and bacterial viruses. The latter are also called bacteriophages ("bacteria eaters"), or simply phages.

Viruses vary considerably in size, shape, and composition (Figure 1.2a-g) and have evolved specific mechanisms to infect a host cell or cells. We will discuss some of these mechanisms in other chapters, but for now, remember that the genetic material of the virus, once it is within the host cell, directs the cellular machinery to produce progeny viruses.

Cells—The Units of Life

After many years of experiments the **cell theory** was put forward in the early nineteenth century. There are three basic tenets of the cell theory:

1. The **cell** is the smallest building unit of a multicellular organism and, as a unit, is itself an elementary organism.
2. Each cell in a multicellular organism has a specific role.
3. A cell can only be produced from another cell by cell division.

Beyond these three basic ideas our knowledge and understanding of the structure of organisms and cells has been advanced through the use of microscopes. Under the microscope we can see that while there is a great diversity of cell types, they all have some features in common. We will start our study of the genetics of various life forms by examining cell structure.

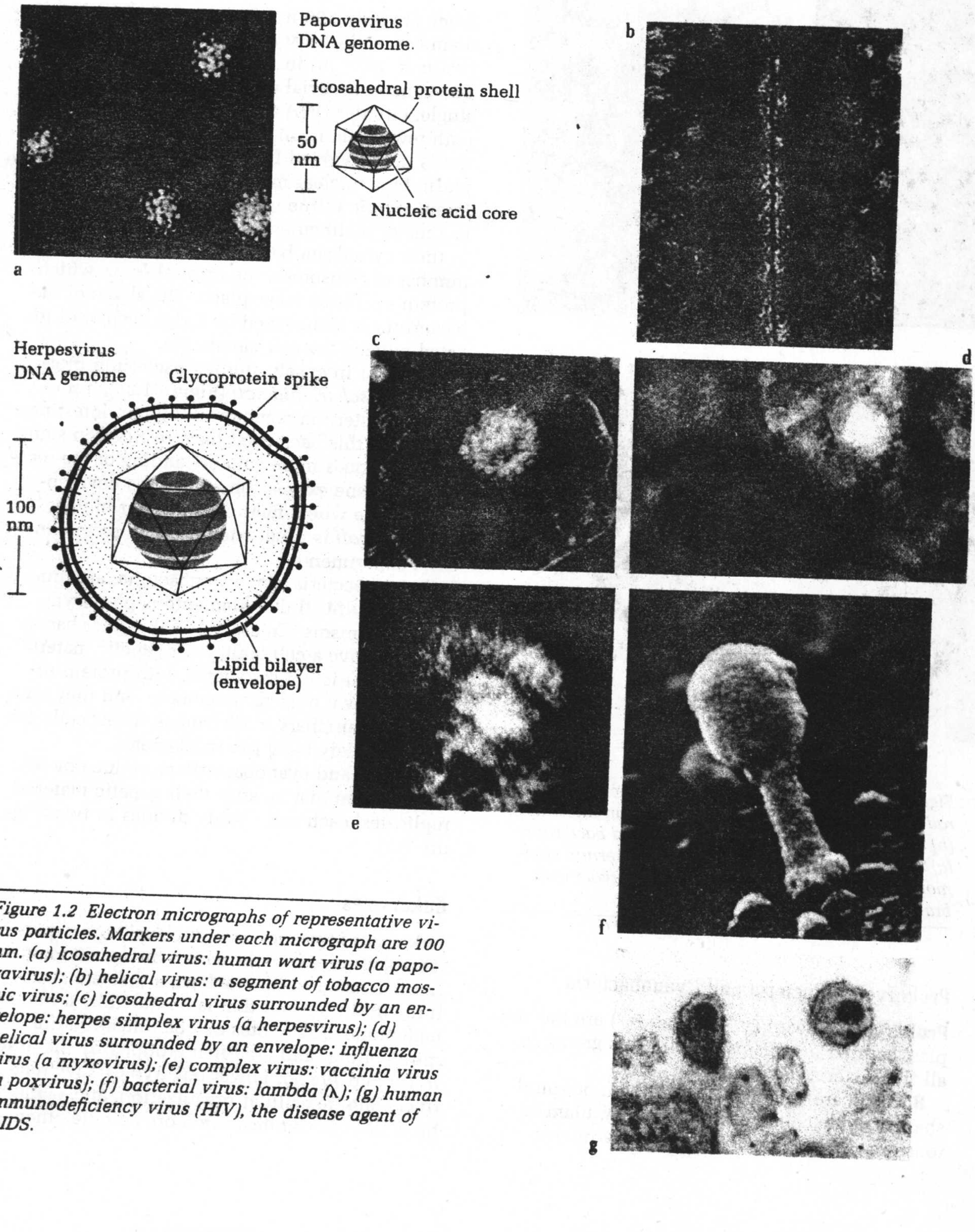

Figure 1.2 Electron micrographs of representative virus particles. Markers under each micrograph are 100 nm. (a) Icosahedral virus: human wart virus (a papovavirus); (b) helical virus: a segment of tobacco mosaic virus; (c) icosahedral virus surrounded by an envelope: herpes simplex virus (a herpesvirus); (d) helical virus surrounded by an envelope: influenza virus (a myxovirus); (e) complex virus: vaccinia virus (a poxvirus); (f) bacterial virus: lambda (λ); (g) human immunodeficiency virus (HIV), the disease agent of AIDS.

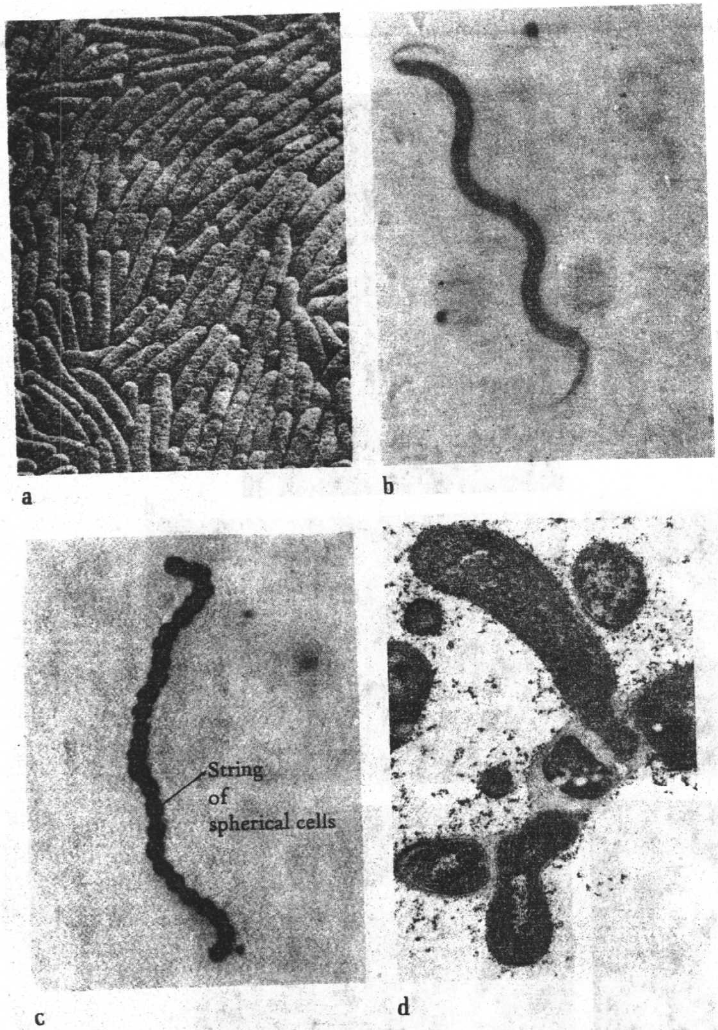

Figure 1.3 Four prokaryotes: (a) Escherichia coli, *a rod-shaped bacterium common in human intestines; (b)* Spirillum volutans, *a helically coiled bacterium; (c)* Streptococcus lactis, *a spherical bacterium common in milk; (d)* Actinomycete, *a prokaryote with branching, multicellular filaments.*

Prokaryotes: Bacteria and Cyanobacteria

Prokaryotes (meaning "prenuclear") are the simplest cellular organisms. Within this group are all the bacteria (Figure 1.3).

Bacteria are spherical, rod-shaped, or spiral-shaped single-celled or multicellular, filamentous organisms (Figure 1.3) that vary in size. Some are only 100 nm (1 nm = 10^{-9} m) in diameter, while very large ones are 6 μm (1 μm = 10^{-6} m) in diameter and 60 μm long. The genetic material of bacteria is found in a single, circular DNA molecule that is associated with few proteins. In bacteria this genetic material is not separated from the rest of the cytoplasm by a nuclear membrane such as is found in eukaryotic ("true nuclear") organisms, which is a major distinguishing feature of prokaryotes. In their cytoplasm bacteria also contain a large number of ribosomes, the organelles on which protein synthesis takes place. The shape of the bacterium is maintained by a rigid cell wall located outside the cell membrane.

The most intensely studied bacterium in genetics is *Escherichia coli* (Figure 1.3a), a rod-shaped bacterium common in human intestines. Studies of this bacterium have resulted in significant advances in our understanding of the regulation of gene expression and in the development of the whole field of molecular biology. Today *E. coli* is used extensively in recombinant DNA experiments.

Certain bacteria, the cyanobacteria, are unicellular or multicellular, filamentous photosynthetic organisms (Figure 1.4). Like other bacteria, they have a cell wall, their genetic material is DNA that is not associated with protein or bounded by a nuclear membrane, and they contain large numbers of ribosomes. Their cells are approximately 6–10 μm in diameter.

Bacteria and cyanobacteria reproduce by **binary fission;** that is, after their genetic material replicates, each cell simply divides in two (Figure 1.5).

Eukaryotes

Eukaryotes (means "true nucleus") are organisms that have cells in which the genetic material is located in the **nucleus,** a discrete structure within the cell that is bounded by a nuclear membrane. Eukaryotes can be unicellular or multicellular and are often grouped by the terms *lower* and *higher*. Lower eukaryotes have relatively simple cellular organization, and while their DNA is significantly more complex than